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(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, New Dehli 110 019 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MURPANI, Deepak** [IN/IN]; C-213, Lajpat Nagar - I, New Delhi 110 024 (IN). **MALIK, Rajiv** [IN/IN]; 6-B, Pocket - B, Gangotri Enclave, Alaknanda, New Delhi 110 019 (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o Deshmukh, Jayadeep, R., Suite 2100, 600 College Road East, Princeton, NJ 08540 (US).

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(54) Title: PROCESS FOR THE PREPARATION OF A FAST DISSOLVING DOSAGE FORM

(57) Abstract: The present invention relates to a process for the preparation of fast dissolving dosage form, such as tablet, which disintegrates quickly in the mouth. The process of this invention is particularly suitable for moisture sensitive, poorly compressible and bitter drugs having a taste mask coating.

PROCESS FOR THE PREPARATION OF A FAST DISSOLVING DOSAGE FORM

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of fast dissolving dosage form, such as tablet, which disintegrates quickly in the mouth. The process of this invention is particularly suitable for moisture sensitive, poorly compressible and bitter drugs having a taste mask coating.

BACKGROUND OF THE INVENTION

Over the past few years, there is an increased interest in fast dissolving or disintegrating pharmaceutical dosage forms because these provide solution to problems faced by pediatric or geriatric patients who have difficulty swallowing conventional tablets or capsules, thereby increasing patient compliance. Similarly, in cases of motion sickness, sudden episodes of allergic attacks, coughing, epileptic seizures or convulsions, fast dissolving dosage forms are highly desirable. They are also useful for the sublingual or buccal administration of drugs.

Fast disintegrating tablets are known to be prepared by tablet molding, spray drying, vacuum drying and freeze drying techniques, to name a few. Currently available fast disintegrating tablets have several limitations such as poor physical integrity; insufficient taste masking; requirement of careful packaging and handling; sensitivity to humidity and temperature; unpleasant mouth-feel; difficulty in high drug loading; requirement of special equipment

like freeze dryer or spray dryer; use of expensive or time consuming processing; and need for special packaging material or equipment.

In tablet molding technique, the powder blend is moistened with a hydro-alcoholic solvent and molded into tablets under pressures lower than those used in conventional tablet compression. The solvent is removed by air drying. However, tablets prepared by molding do not have sufficient mechanical strength. Additionally, molded tablets exhibit poor taste-masking characteristics. To overcome this, U.S. Patent No. 5,082,667 discloses the incorporation of drug-containing discrete particles, formed by spray-congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol, and an active ingredient into a lactose-based tablet triturate form. The tablet triturate is limited to active ingredients, such as estozolam, that are not sensitive to the melting temperature of the glyceride. Further, since the dosage form is formed into a damp mass and subsequently dried, conventional compression tabletting machines cannot be used to manufacture this product.

U.S. Pat. No. 5,466,464 describes a process, using an agar solution as a binding agent and a blister - packaging well as a mold to prepare an intra-buccal fast-disintegrating tablets. The process involves the preparation of a suspension containing active, agar and sugars, filling the suspension into the well, solidifying at room temperature and drying at 30ºC under a pressure of 700 to 760mm Hg.

U.S. Pat. No. 5,298,261 describes a vacuum drying process to prepare rapidly disintegrating tablets. Vacuum drying a frozen mixture containing a gum, carbohydrates and a solvent in a tablet shaped mold produced tablets with enhanced structural integrity compared with that of traditional molded tablets. However, there is always a risk of residual solvents in the tablets prepared by this method.

Spray drying technique described in U.S. Pat. Nos. 5,587,180; 5,595,761, 5,635,210 and 5,807,576 is another technique used to prepare fast dissolving tablets. These formulations incorporated hydrolyzed and non-hydrolyzed gelatin as support agents, mannitol as a bulking agent, sodium starch glycolate or croscarmellose sodium as a disintegrant, and an effervescent couple to enhance disintegration and dissolution. Tablets made from the spray dried powder disintegrate within 20 seconds when immersed in an aqueous medium.

A more recent approach is the technology described in U.S. Pat. Nos. 5,178,878 and 5,503,846. These patents describe an oral dosage form, which involves incorporating micro-encapsulated drug ingredients into a tablet that dissolves in the mouth without the need for chewing or water. Moreover, they use evolution of carbon dioxide as a disintegration mechanism. These tablets are obtained by compression and packed into special peel-off blister packs as their mechanical resistance is insufficient and they are sensitive to moisture. It takes 15 to 60 seconds to dissolve in the mouth, which is longer than is desired.

U.S. Pat. Nos. 4,855,326, 5,587,172, 5,622,719, 5,866,163 and 5,869,098 assigned to Fuisz use a precision-engineered, rapidly spinning machine to convert a unique mixture of a spinnable carrier agent such as sugar and other processing aids into candy floss

U.S. Pat. No. 5,576,014 describes a fluidized-bed granulation technology for WOWTAB quick-dissolving, without water tablets.

U.S. Pat. Nos. 4,305,502; 4,371,516; 5,738,875 use lyophilization (freeze drying) process to make an amorphous, porous structure which dissolves rapidly. The principle of this technology (Zydis, technology) consists of preparing an aqueous suspension of the active ingredient and the excipients, which is dispensed into blister packs and water is removed by a freeze drying process. The final product is obtained by sealing the dried product in special peel-off blister packs. The effectiveness of a freeze-drying process depends on the physico-chemical parameters of active substances used. This technology is ideally suited for the drugs which are relatively water-insoluble, of low dose and of fine particle size to allow formation of a stable aqueous suspension with the matrix components. Problems may arise with soluble drugs due to the formation of eutectic mixtures lowering the freezing point of the formulation, resulting in incomplete freezing or melting during drying, which can result in the loss of the product. Similarly, the development of dosage forms having high concentration of active is difficult with this technology. However, a major disadvantage of this technology is the time consuming and costly freeze drying process.

U.S. Pat. No. 6,083,531 describes an improved technique for preparing a rapidly dispersing tablet by preparing a suspension or solution of the active ingredient by dispersing or dissolving it in a solvent together with all other components of the composition and dispensing into molds e.g. blisters and then drying either by simple storage at room temperature or at elevated temperatures or by microwave radiation either at normal pressure or at reduced pressure. However, the risk of residual solvent in the final dosage form can not be ruled out.

U.S. Pat. No. 5,853,758 provides a method for the preparation of a tablet of increased strength which comprises the steps of (a) combining and compressing a meltable binder and the active agent into a tablet (b) melting said binder in the tablet and (c) solidifying the binder by cooling. Further, volatile substances are added to increase the porosity. Method provides better hardness and friability but increases the disintegration time.

SUMMARY OF THE INVENTION

The present invention addresses the drawbacks and problems associated with the currently available technologies. It avoids the use of expensive and non-conventional equipment like freeze dryer or spray dryers. It also avoids the time consuming conventional process like compression.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process of preparing fast dissolving dosage form for oral administration, comprising the steps of

a. Blending a pharmaceutically active ingredient, a cementing agent and optionally, together with other pharmaceutical excipients;

b. filling or dispensing the powder blend into the mold/final pack;

c. heating the powder blend; and

d. allowing it to cool to ambient temperature to make the dosage form in-situ.

The process of the present invention is simple as it requires less number of steps than required in the conventional tabletting methods and is suitable for broad range of active ingredients with varying physico-chemical properties. It is particularly suitable for moisture sensitive drugs because the process does not involve the use of any solvent medium. It is also suitable for the poorly compressible drugs, as the binding is provided by fusion with cementing agent rather than compression; and the bitter drugs having a taste mask coat because the process does not involve compression leaving the coating intact.

Moreover, as no solvent is used in the process of the present invention, the final dosage form is at least as free of residual solvents as the starting active ingredient. Furthermore, as the dosage form is made in-situ in the mold/final pack, the low hardness and high friability problems normally associated with the fast dissolving dosage forms do not arise. The dosage

form prepared by the present invention does not require any special packing like "peel on" etc. It has sufficient mechanical strength to withstand the usual press through pack (blister packaging).

Therefore, the present invention provides a process for preparing a solid pharmaceutical dosage form adapted for direct usual administration into the mouth, which is particularly useful for improving compliance in geriatric and pediatric patients who have difficulty in swallowing.

The cementing agent of the present invention provides cohesive properties to the powdered material on heating and thereby fuses the powder blend when allowed to cool to make the tablets in-situ. Further, it ensures that the tablet remains intact. The cementing agent of the present invention can be selected from the excipients well known in the art. Preferably, it is selected from the pharmaceutical binders which melt on heating. The preferred cementing agent of the present invention melts at a temperature ranging from about 20ºC to about 100ºC, preferably from about 40ºC to about 60ºC. The cementing agent of the present invention may include fats such as lanolin, lanolin alcohol, hydrous lanolin; natural waxes such as carnuba wax; natural or synthetic polymers such as polyethylene glycols (PEGs); maltodextrins; and sugars such as dextrose and xylitol.

The cementing agent is selected in a way such that it melts at a temperature lower than the decomposition temperature of the pharmaceutically active agent and excipients present. The preferable cementing agents of this invention are PEGs, having molecular weights

ranging from 200 to 20,000; preferably from 1000 to 8000. Solid PEGs are preferred. Mixture of PEGs of different molecular weights or a mixture of liquid and solid grade PEGs are also contemplated. A structural body having desired hardness and disintegration / dissolution rate can be obtained regardless of their mixing ratio. However, such a structure of interest can not be obtained with usual pharmaceutical binders such as polyvinylpyrrolidone, xanthan gum, guar gum and the like, if used alone. However, they can be used together with PEGs to increase the cohesiveness.

The polyethylene glycol forms the desired shape because it melts on heating and therefore fuse all the components of the dosage form when allowed to cool acquire the shape of the mold/pack. Different molecular weight PEGs can be combined to give good dispersibility and solubility.

Though the concentration and molecular weight may vary depending upon the active ingredient and the desired hardness, the PEGs may be used in the inventive process in a concentration of upto 90 w/w%, preferably 20 w/w% or more, based on the total weight of the dosage form.

The cementing agent may be combined with the other excipients and the pharmaceutically active agent in any sequence.

The excipients of the present invention may be selected from the diluent, binder, disintegrants, flow promoters/antiadherents, flavors and sweetening agents. The diluent of the present invention may be selected from water soluble diluents well known in the art such as mannitol, lactose, sucrose, glucose, fructose, sorbitol, xylitol, calcium sulfate, calcium carbonate,

microcrystalline cellulose and maltodextrin. Preferred diluents are mannitol and sorbitol as they form the low density matrix which disintegrates rapidly within the mouth. The diluent is usually present in an amount of upto 90 weight percent, preferably upto 70 weight percent.

A suitable binder may be added to further improve the cohesive properties of the formulation. Binders may include starch; gelatin; sugars such as molasses, lactose, glucose, dextrose and sucrose; natural and synthetic gums such as acacia, sodium alginate, carboxymethyl cellulose, methylcellulose, polyvinyl pyrrolidone and veegum.

Disintegrating agents may be selected from celluloses such as croscarmellose sodium, starches such as potato starch, clay such as bentonite, gums such as sodium alginate, polymers such as hydroxypropyl methyl cellulose and effervescent agents such as citric acid and sodium bicarbonate.

Flow promoters / anti-adherents may be selected from magnesium stearate, talc, aerosil and sodium stearyl fumarate.

Excipients, such as coloring agents, flavoring agents, artificial sweeteners; having acceptable food and drug approval and which are compatible with the cementing agent and active, can be included.

Active substances may be selected from the pharmaceuticals but may also include vitamins, minerals or dietary supplements. Pharmaceuticals may include antacids such as omeprazole, non-steroidal anti-inflammatory drugs

such as rofecoxib and nimesulide, steroidal anti-inflammatory drugs such as betamethasone, anti-psychotic drugs such as olanzapine, hypnotic drugs such as alprazolam, antiepileptic drugs such as sodium valproate, antiparkinsonism drugs such as levodopa, hormone drugs such as progestin, analgesic drugs such as aspirin, serotonin 5HT receptor antagonists such as ondansetron, diuretic drugs as sulphamethoxazole, coronary vasdilators such as nitroglycerin, H2 receptor antagonists such as ranitidine hydrochloride, antiarrhythmic drugs such as pindolol, cardiotonic drugs such as digitoxin, calcium antagonists such as diltiazem hydrochloride, antihistaminic drugs such as fexofenadine hydrochloride, antibiotics such as doxycycline, antitumor drugs such as actinomycin, antidiabetic drugs such as metformin, gout treating drugs such as allopurinol, antiallergic drugs such as loratadine, antihypertensive drugs such as quinapril, central nervous system acting drugs such as indeloxazine hydrochloride, antispasmodic drugs such as butylscopolamine, antihyperlipidemic drugs such as simvastatin, bronchodilators such as salbutamol, α-adrenergic receptor blockers such as tamsulosin hydrochloride, osteoporosis treating drugs such as sodium alderonate, antifungal drugs such as fluconazole, antivirals drugs such as lamivudine, drugs for erectile dysfunction such as sildenafil and antidepressant such as sertraline.

The active ingredients are not particularly limited to the above examples, and not only to pharmaceutical drugs but also various other substances such as diagnostic drugs, food and dental plaque disclosing agent

can be applied to the preparation of the present invention. Active substances can be coated, if desired. Active substances may have a taste mask coating.

The inventive process of the present invention comprises uniform blending of the pharmaceutically active ingredient with the cementing agent, and the optional excipients such as diluent, binder, disintegrant, sweetener, flavoring agent and flow enhancer. The powder blend is sieved through fine mesh to obtain fine powder and volumetrically filled into the mold/final pack. Filling may be done manually, semi-automatically or automatically. The powder blend can be pressed slightly after filling inside the mold/pack either by manual or automatic tapping or rollers. The powder blend can be granulated before filling, if desired. Filled final packs are either sealed first and heated or heated as such.

Heating may be done at about 25ºC to about 80ºC, but preferably at about 50ºC to about 60ºC. The mold to be used is not particularly limited, and those made of metals or resin films may be used. A preferred mold is a resin film sheet having a number of hollows, which is used for the enclosure of tablets by Press Through Pack (blister packaging). After filling in the resin film sheet, a cover sheet for use in usual Press Through Pack (blister packaging) is adhered to the resulting resin film sheet, thereby, easily obtaining packages of the solid preparation of the present invention. The material of the sheet has no particular limitation, and may be selected from polypropylene, polyvinyl chloride, polyvinylidene chloride and the like. Though the shape of the mold is not particularly limited, the hollow of the mold may preferably have a globular shape.

After heating, the molds / packs are allowed to cool to ambient temperature.

The dosage forms prepared by the present inventive process disintegrates when taken into the mouth within about 15 seconds, preferably within about 10 seconds and especially within about 5 seconds because of its highly porous nature and there is no after taste or grittiness.

The present invention is illustrated by, but is by no-means limited to, the following examples.

EXAMPLE 1

Mouth dissolving tablets of Rofecoxib.

Ingredient	**mg/unit**
Rofecoxib	25.0
Aspartame	1.0
Orange flavour	2.0
Croscarmellose sodium	9.0
PEG 8000	60.0
Sorbitol	233.0
Total weight	330.0

Rofecoxib, aspartame, orange flavour, croscarmellose sodium, PEG 8000 and sorbitol are sifted through (60 BSS) sieve and mixed. The powder is dosed by weight / volume into preformed blisters. Blisters are sealed using an appropriate covering sheet such as aluminium foil or aluminium foil paper laminates. After sealing, blister strips are heated at about 60ºC for approx. 10 minutes and allowed to cool to room temperature.

EXAMPLE 2

Mouth dissolving tablets of Rofecoxib.

Ingredient	mg/unit
Rofecoxib	25.0
Aspartame	1.0
Orange flavour	2.0
Croscarmellose sodium	9.0
Calcium carbonate	15.0
Monosodium citrate	15.0
PEG 8000	60.0
Sorbitol	203.0
Total weight	330.0

Rofecoxib, aspartame, orange flavour, croscarmellose sodium, calcium carbonate, monosodium citrate, PEG 8000 and sorbitol, sifted through 60 BSS sieve and mixed for 10 minutes. Adequate aliquots of the powder blend are dispensed into hollows of a sheet for Press Through Pack (blister packaging). An aluminium sheet is adhered to each of the powder blend containing sheets for blister pack.

Sealed blister strips are heated at about 60ºC for approx. 15 minutes and allowed to cool to room temperature.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We claim:

1. A process for preparing a fast dissolving solid pharmaceutical dosage form, for oral administration, comprising the steps of

   a. blending

      - a pharmaceutically active agent,

      - a cementing agent, and

      - optionally, other pharmaceutical excipients.

   b. filling the powder blend of step (a) into the mold/final pack;

   c. heating the powder blend; and

   d. allowing it to cool to ambient temperature to make the dosage form in-situ.

2. The process according to claim 1 wherein the dosage form is a tablet.

3. The process according to claim 2 wherein the tablet dissolves in the mouth.

4. The process according to claim 1 wherein the powder blend is pressed after filling.

5. The process according to claim 1 wherein the powder blend is granulated before filling.

6. The process according to claim 1 wherein the heating is done at 25-80ºC temperature.

7. The process according to claim 1 wherein one or more pharmaceutical active ingredient is selected from the group consisting of antacids, non-steroidal anti-inflammatory drugs, steroidal anti-inflammatory drugs, anti-psychotic drugs, hypnotic drugs, antiepileptic drugs, antiparkinsonism drugs, hormone drugs, analgesic drugs, serotonin 5HT receptor antagonists, diuretic drugs, coronary vasdilators, H2 receptor antagonists, antiarrhythmic drugs, cardiotonic drugs, calcium antagonists, antihistaminic drugs, antibiotics, antitumor drugs, antidiabetic drugs, gout treating drugs, antiallergic drugs, antihypertensive drugs, central nervous system acting drugs, antispasmodic drugs, antihyperlipidemic drugs, bronchodilators, α-adrenergic receptor blockers, osteoporosis treating drugs, antifungal drugs, antivirals drugs, drugs for erectile dysfunction and antidepressant.

8. The process according to claim 7 wherein the pharmaceutically active ingredient is selected from the group consisting of omeprazole, rofecoxib, nimesulide, betamethasone, olanzapine, alprazolam, sodium valproate, levodopa, progestin, aspirin, ondansetron, sulphamethoxazole, nitroglycerin, ranitidine hydrochloride, pindolol, digitoxin, diltiazem hydrochloride, fexofenadine hydrochloride, doxycycline, actinomycin, metformin, allopurinol, loratadine, quinapril, indeloxazine hydrochloride, butylscopolamine, simvastatin, salbutamol,

tamsulosin hydrochloride, sodium alderonate, fluconazole, lamivudine, sildenafil and sertraline.

9. The process according to claim 1 wherein the pharmaceutically active ingredient may be coated.

10. The process according to claim 9 wherein the active ingredient has a taste mask coating.

11. The process according to claim 1 wherein the cementing agent is a pharmaceutical binder which melts on heating.

12. The process according to claim 11 wherein the cementing agent melts to fuse the components of the dosage form.

13. The process according to claim 11 wherein the cementing agent comprises fats, natural waxes, natural or synthetic polymers, maltodextrins and sugars.

14. The process according to claim 13 wherein the cementing agent is selected from a group consisting of lanolin, lanolin alcohols, hydrous lanolin, carnuba wax, polyethylene glycol, dextrose, xylitol, and mixtures thereof.

15. The process according to claim 14 wherein the polyethylene glycol may be a mixture of high and low molecular weights polyethylene glycols.

16. The process according to claim 1 wherein the pharmaceutical excipients comprises a diluent, binder, disintegrant, flow promoter / anti-adherent, sweetener, or a flavoring agent.

17. The process according to claim 16 wherein the diluent is selected from the group consisting of mannitol, lactose, sorbitol, xylitol, glucose, fructose, calcium sulphate, calcium phosphate, polyethylene glycol, and maltodextrin.

18. The process according to claim 16 wherein the disintegrants comprises celluloses, starches, clay, gums, polymers, and effervescent agents.

19. The process according to claim 18 wherein the disintegrants are selected from the group consisting of croscarmellose sodium, potato starch, bentonite, sodium alginate, hydroxy propyl methyl cellulose, citric acid and sodium bicarbonate.

20. The process according to claim 16 wherein the flow promoters / anti-adherents, are selected from the group consisting of talc, stearic acid, magnesium stearate, aerosil and sodium stearyl fumarate.

21. The process according to claim 16 wherein the sweetener is aspartame.

22. The process according to claim 1 wherein the mold may be made of metals or resins films.

23. The process according to claim 1 wherein the final packs are blister packs.

24. The process according to claim 23 wherein the material of blister pack is selected from the group consisting of polypropylene, polyvinylchloride, polyvinylidene chloride and the like.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,866,163 A (MYERS et al.) 02 February 1999 (02.02.1999), see columns 6-9, 11-12, examples, and claim 8.	1-22
X	US 6,083,531 A (HUMBERT-DROZ et al.) 04 July 2000 (04.07.2000), see abstract, columns 2-4, and example.s	1-20, 23
X	US 4,946,684 (BLANK et al.) 07 August 1990 (07.08.1990), see columns 2-4, and examples	1-20, 23
Y	US 5,631,023 (KEARNEY et al.) 20 May 1997 (20.05.1997), columns 5-7, examples.	1,23, 24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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